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DENTONS US LLP
P.O. BOX 061080
CHICAGO, IL 60606-1080

EXAMINER
DEVEAU ROSEN, JASON

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte THOMAS M. MALVAR, SHIHSHIEH HUANG, and MICHAEL H. LUETHY[1]

Appeal 2016-001196
Application 12/909,466
Technology Center 1600

Before MELANIE L. McCOLLUM, JOHN G. NEW, and RACHEL H. TOWNSEND, *Administrative Patent Judges*.

TOWNSEND, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to corn meal, which have been rejected as obvious. We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.

STATEMENT OF THE CASE

Corn "is a grain widely used as animal feed." (Spec. 2.) There are ten amino acids that are "deemed essential in a mixed grain feed" including lysine, methionine, and threonine, and "corn is particularly lacking" in those

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[1] Appellants identify the Real Party in Interest as Monsanto Company, the parent company of the assignee Monsanto Technology LLC. (Appeal Br. 2.)

essential amino acids. (*Id.*) Thus, feed corn is supplemented with these nutrients. (*Id.* at 2–3.) Lysine is "often provided by the addition of soybean meal or synthetic lysine." (*Id.* at 3.) Appellants' Specification indicates that "[i]t would be of benefit to the art to increase the level of lysine in corn seed as a means of making the seed more nutritious as a food or feed grain." (*Id.*) Appellants' invention is directed at corn meal from transgenic corn seed that has "increased levels of lysine in the seed." (*Id.* at 4.)

Claims 39, 42, 48–51, and 53–56 are on appeal. Claim 39 is representative and reads as follows:

> 39. Corn meal prepared from bulked transgenic corn seeds, said corn seeds comprising a heterologous expression cassette comprising SEQ ID NO:1 and 4000 ppm to 6500 ppm free lysine, wherein no lysine is added to said meal, and wherein said corn meal has elevated lysine as compared to a meal processed in the same manner from corn seeds of a control plant not comprising the heterologous expression cassette.

(Appeal Br. 14.)

The following ground of rejection by the Examiner is before us on review:

Claims 39, 42, 48–51, and 53–56 under 35 U.S.C. § 103(a) as unpatentable over Falco '019,[2] Bailey,[3] and Falco '831.[4]

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[2] Falco et al., US 6,459,019 B1, patented Oct. 1, 2002.
[3] Bailey et al., US 2005/0255568 A1, published Nov. 17, 2005.
[4] Falco et al., WO 98/42831, published Oct. 1, 1998.

DISCUSSION

The Examiner finds that Falco '019 teaches that human food and animal feed derived from corn are limited in lysine, which is an important dietary requirement. (Final Action 5.) According to the Examiner, Falco '019 teaches it would be desirable to increase the lysine content of corn seed to eliminate the need to supplement mixed grain animal feeds with lysine produced by fermentation microbes. (*Id.*; Ans. 10.) The Examiner finds that Falco '019 teaches producing corn seeds with increased free-lysine. (Final Action 4.) In particular, the Examiner finds that Falco '019 teaches co-expressing lysine insensitive DHDPS and lysine insensitive lysC-M4 gene (which corresponds to the aspartate kinase (AK) gene) in the corn seed embryo and that this produces corn seeds with free lysine levels that are greater than control seeds that do not express a lysine insensitive DHDPS. (*Id.*) According to the Examiner the co-expression of these two genes in the embryo resulted in an increase in free lysine of 15–27% of free amino acids compare to the control 1.4% of free amino acids. (*Id.*)

The Examiner further finds that Falco '019 teaches that as corn endosperm lysine catabolism is expected to be much greater than in the embryo, and thus with respect to corn endosperm, it is preferable to express both lysine insensitive DHDPS and lysine insensitive AK and also inhibit lysine catabolism by reducing the level of LKR. (*Id.*)

The Examiner finds that Falco '831 teaches that "LKR is a bifunctional enzyme that is responsible for the catalysis of the first and second reaction in the catabolism of lysine," "and that antisense LKR RNA

or co-suppression of LKR can be achieved . . . to reduce the loss of lysine due to catabolism." (*Id.* at 5–6.)

The Examiner finds in light of the two Falco references that it would have been obvious to one of ordinary skill in the art to co-transform a corn plant with nucleic acid sequences encoding a DHDPS and an AK gene as taught by Falco '019 and a nucleic acid sequence encoding an RNA molecule to suppress expression of a LKR gene as taught by Falco '831 to achieve further increase in free lysine by reducing the loss of lysine due to catabolism. (*Id.* at 7.)

The Examiner further finds that Bailey teaches a DHDPS with reduced feedback inhibition that has 99% identity to SEQ ID NO: 1 recited in Appellants' claim 39. (Final Action 5.) The Examiner further finds that Bailey teaches that when this is expressed in bacterial strains it results in increase in the production of amino acids of the aspartic acid family having reduced feedback inhibition. (Final Action 5.) The Examiner explains that while the sequence identity is not 100%, the difference is a single conservative mismatch at base pair position 3, and the DHDPS polypeptide encoded by that sequence has 100% identity with the lysine insensitive DHDPS disclosed to be encoded by SEQ ID NO: 1. (*Id.*; Ans. 9.) The Examiner, thus, concludes that the sequence encoding DHDPS with reduced feedback disclosed in Bailey is a functional equivalent to the claimed SEQ ID NO: 1. (Final Action at 6.)

In light of Bailey's teaching, the Examiner further concludes that it would have been obvious to one of ordinary skill in the art to substitute the functional equivalent sequence disclosed in Bailey for the DHDPS sequence

disclosed in Falco '019 (modified to also include a nucleic acid sequence encoding an RNA molecule to suppress expression of a LKR gene as taught by Falco '831), "because Falco ['019] teach that DHDPS can be isolated from other sources, and because said method would predictably lead to an increase in the lysine content of a transgenic corn seed." (*Id.*)

The Examiner also concludes that one of ordinary skill in the art would have a reasonable expectation of success in arriving at a corn seed comprising 4000 ppm to 6500 ppm free lysine because the corn seed would have the claimed structural features. (Final Action 6–7, 8; Ans. 8, 11–13.)

We agree with the Examiner's conclusion of obviousness. Falco '019 and Falco '831 teach that antisense LKR RNA can be used to reduce the loss of lysine due to catabolism, and both teach a chimeric gene construct where the LKR sequence is linked to genes encoding lysine insensitive DHDPS and are introduced to plants via transformation simultaneously. (Falco '019 26; Falco '831 10, 35, 98.) Both Falco references also teach that preventing lysine catabolism by reducing or eliminating LKR expression or activity in the endosperm along with expression of both *Corynebacterium* DHDPS and the *E.coli* AKIII-M4 in the endosperm should "achieve significant lysine increases in the endosperm." (Falco '019 26: 13–15, Falco '831 31.)

Appellants argue that the prior art does not specify or suggest transgenic corn seeds comprising 4000 to 6500 ppm free lysine, or meal or product produced therefrom. (Appeal Br. 5.) There is no dispute that the references do not show transgenic corn seeds comprising 4000 to 6500 ppm free lysine. However, the Examiner's rejection was based on a combination of three prior art references that when combined provide for the identical

structure that Appellants' Specification teaches achieves the foregoing production. (Spec. 27–29 (Table 1 (entries 4, 7, 15, and 30).) While the prior art may not have suggested the combination for the achievement of precisely the claimed amount of free lysine claimed, "the law does not require that the references be combined for the reasons contemplated by the inventor." *In re Beattie,* 974 F.2d 1309, 1312 (Fed. Cir. 1992.) We agree with the Examiner that the prior art provides a reason to make a transgenic corn seed with a reasonable expectation of success that incorporates lysine insensitive DHDPS, lysine insensitive AK, and mRNA of LKR. Moreover, such transgenic corn seeds would have the structure that Appellants' Specification indicates achieves the claimed amount of free lysine. And, as the Examiner found, a corn meal or product produced therefrom is also reasonably suggested by the prior art.

Falco '019 indicates that increases in the "lysine content of . . . corn . . . would reduce or eliminate the need to supplement mixed grain feeds with lysine produced via fermentation of microbes." (Falco '019 1:35–38.) Falco '019 and '831 provide a compelling motivation to add a chimeric gene for antisense LKR to a gene encoding a lysine-insensitive DHDPS (with or without a lysine-insensitive AKIII) to significantly improve free lysine.

Falco '019 indicates that a 27% increase is achievable just by introducing a lysine-insensitive DHDPS into the embryo. (Falco '091 (Example 26 and Table 12).) Falco '019 shows that corn seed where the endosperm was transformed with a lysine-insensitive DHDPS and AKIII-M4 did not achieve the increase in free amino acid that was achieved with

corn seed where the embryo was transformed with only a lysine-insensitive DHDPS. However, Falco '019 specifically teaches that there was lysine catabolism in the embryo and even higher lysine catabolism is expected in the endosperm, which "probably prevents the accumulation of increased levels of lysine in seeds expressing [a lysine-insensitive DHDPS and lysine insensitive lysC-M4] from the glutelin 2 promoter [in the endosperm]." (Falco '019 92 (Example 26).)[5] Falco '831 and Falco '019 both suggest that preventing lysine catabolism by reducing or eliminating enzyme function in the plant gene that encodes LKR should increase accumulation of excess free lysine that is accomplished by the introduction of lysine insensitive DHDPS with or without lysine insensitive lysC-M4 introduction to the plant seed. (Falco '019 3:47–55, 9:49–65; 26:12–43 (noting that preventing lysine catabolism is desirable "to accumulate higher levels of free lysine" and that "to achieve significant lysine increases in the endosperm it is preferable to

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[5] Appellants' assertion that "the 130% increase in free lysine seen in corn seeds expressing DHDPS **is completely eliminated** in seeds expressing DHDPS and AK" (Reply Br. 5, 6) is not altogether accurate. Notably Table 12 of Falco '019 demonstrates that the expression of lysine insensitive DHDPS alone in the endosperm, like the expression of lysine insensitive DHDPS with AK in the endosperm, also resulted in the failure to accumulate increased free lysine. What Falco '019 demonstrates in Table 12 is that the 130% increase in free lysine seen in corn seeds whose embryo expressed lysine insensitive DHDPS is not seen in seeds whose endosperm, but not embryo, express lysine insensitive DHDPS and AK. Falco '019 attributes this observation to a greater lysine catabolism by LKR in the endosperm where the lysine insensitive DHDPS and AK were expressed rather than to any combination of expression of lysine insensitive DHDPS and AK as compared to the expression of lysine insensitive DHDPS alone. (Falco '019 92:53–61.)

express both *Corynebacterium* DHDPS and the *E. coli* AKIII-M4 in the endosperm and to reduce lysine catabolism by reducing the level of lysine ketoglutarate reductase"); Falco '831 9–10, 31.) As the Examiner found, which Appellants' do not dispute, Falco '831 teaches "a nucleic acid sequence having 96% identity to SEQ ID NO: 2 of the instant invention" (Final Action 5), which "encodes a lysine ketoglutarate reductase" that can be used to design inhibitory RNA's (Spec. 5.) Moreover, Falco '019 and '831 teach one of ordinary skill in the art how to use such sequences to create a chimeric gene designed to express antisense RNA for all or a part of the LKR gene to down-regulate the LKR activity. (Falco '019 75, Falco '831 98.)

Endosperm-specific promoters were known. (Falco '019 19:28–40 (referencing the known 10 kD, 27 kD and 19 kD zein storage proteins).) And Falco '019 teaches that using such endosperm-specific promoters, one can obtain expression of protein in the endosperm. (Falco '019 Example 26 and Table 12 (last entry, noting glutelin 2 promoter expressed lysine insensitive DHDPS and lysine insensitive lysC/AKIII-M4 in the endosperm).) Thus, one of ordinary skill in the art would reasonably expect from the teachings of Falco '019 and '831 that an antisense LKR could be expressed in corn endosperm along with lysine insensitive DHDPS and lysine insensitive lysC/AKIII-M4, which, as suggested by Falco '019, would allow for the increased accumulation of lysine promoted by the expression of lysine insensitive DHDPS and lysine insensitive lysC/AKIII-M4 in the endosperm to remain without being catabolized.

With respect to the claimed SEQ ID NO: 1, which encodes lysine insensitive DHDPS (Spec. 5), we agree with the Examiner that it would have been obvious to provide the functional variant taught by Bailey (having 99% identity with SEQ ID NO: 1 but 100% amino acid identity (c*ompare* Bailey Table 16 (SEQ ID NO: 126) *with* SEQ ID NO: 7) as the sequence encoding lysine insensitive DHDPS. Bailey teaches that homologous nucleotide sequences that are not identical but are functional variants are embodied within the scope of the sequences taught. (*See* Bailey ¶¶ 209, 213.) Consequently, while Appellants are correct that Bailey does not literally disclose SEQ ID NO: 1 (Appeal Br. 7; Reply Br. 5–6), the difference of the single conservative mismatch at base pair position 3 is not a critical difference for the reason the Examiner expressed, *i.e.*, the encoded amino acid sequence is 100 % identical. And Bailey contemplates a functional variant of the disclosed DNA sequence that results in the identical amino acid sequence that SEQ ID NO: 1 encodes.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). Appellants argue that the achievement of free lysine in the range of 4000 ppm to 6500 ppm is a "surprising result[]" because it represents "more than an order of magnitude greater lysine levels in seeds than the 130% increase in seed lysine values shown by Falco ('019)." (Appeal Br. 10, 12 (citing Declaration by Dr. Huang dated 2014); Reply Br. 4.) We do not find this argument persuasive. "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained

and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). While Falco '019 exemplifies transgenic corn seed that includes lysine insensitive DHDPS in the embryo, Falco '019 and Falco '831 describe transforming corn via introduction of "a chimeric gene for cosuppression of LKR or antisense LKR" along with either "a chimeric gene encoding substantially lysine-insensitive DHDPS" (Falco '831 35), or "chimeric genes encoding substantially lysine-insensitive DHDPS and AK" (Falco '019 9:42–67 and 28:1–9), the cosuppression or antisense LKR gene could be linked to the chimeric gene(s) encoding substantially lysine-insensitive DHDPS or lysine-insensitive DHDPS and AK (Falco '831 35; Falco '019 28:1–9). The comparison Appellants and Appellants' Declarant rely on is the transgenic corn seed that that includes lysine insensitive DHDPS in the embryo or lysine insensitive DHDPS and AK in the endosperm demonstrated in Table 12 of Falco '019 (Appeal Br. 11–12; Appeal Br. Ex. D ¶ 9), and not the described corn transformed via introduction of "a chimeric gene for cosuppression of LKR or antisense LKR" along with "chimeric genes encoding substantially lysine-insensitive DHDPS and AK" (Falco '019 9:42–67 and 28:1–9). Consequently, neither Appellants nor Appellants' Declarant have compared the claimed invention to the closest prior art.

For the foregoing reasons, Appellants do not persuade us that the Examiner erred in rejecting claim 39 for obviousness over Falco '019, Bailey, and Falco '831.

Claims 42, 48–51, and 53–56 have not been argued separately and therefore fall with claim 39. 37 C.F.R. § 41.37(c)(1)(iv).

SUMMARY

We affirm the rejection of claims 39, 42, 48–51, and 53–56 under 35 U.S.C. § 103(a) as unpatentable over Falco '019, Bailey, and Falco '831.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED